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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

WALICKA, MALGORZATA A

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 12/03/2002

(1)

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Applicati n N .

09/720,583

Applicant(s)

POUWELS ET AL.

Examiner

Malgorzata A. Walicka

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-- The MAILING DATE of this communication appears n the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____ .
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-42 is/are pending in the application.
- 4a) Of the above claim(s) 1-27 and 30-42 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 28 and 29 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____ .
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) Z .
- 4) ☐ Interview Summary (PTO-413) Paper No(s). ____ .
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other: *allowable subject matter* .

The response to the Restriction Requirement and Amendment filed on Sep. 25, 2002 as paper No. 10 is acknowledged. Amendment to claim 28 has been entered as requested. Claims 1-42 are pending. Claims 28 and 29 are the subject of this Office Action; claims 1-27 and 30-42 are withdrawn from consideration as directed to the non-elected invention.

Detailed Office Action

1. Restriction /Election

Applicant's election with traverse of Group V, claims 28 and 29 in Paper No. 10 is acknowledged.

Applicants' arguments are that the present application does not lack unity of invention, because the claims are directed to a vector comprising one or more genes to be expressed, therefore the inventive concept is formed by the vector.

Applicants' arguments have been found persuasive in respect to Group I (claims 1-19, and Group II (claim 20), which are rejoined and comprise the new Group I. Groups III-XIII are not rejoined, because, as indicated in the restriction requirement paper No. 9, they are directed to multiple products and methods of use of said vector, and 37 CFR 1.475 does not provide for multiple products or methods within a single application. Thus the restriction is proper and **MADE FINAL**.

Claims 1-27 and 30-42 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Claims 28 and 29 are the subject of examination on merits.

2. Objections

The specification is confusing regarding frequency of transformants that efficiently produce vitamin B₁₂, as well as the actual increase in production of vitamin B₁₂ above the level characteristic for non-transformed *Propionibacterium*.

In Example 4, on page 23, line 1, Applicants write, "Eight out of 10 transformants gave up to a 50% higher vitamin B₁₂ content than the control strain."

In Example 5, on page 25, line 15, Applicants inform, "Nine out of 10 transformants showed approx. 25% higher vitamin B₁₂ production than the control strain."

The specification is objected to, because there is a typographical error on page 5 line 1: 1.7b, which should be 1.7 Kb.

The address of ATCC on page 18, line 7 should be AMERICAN TYPE CULTURE COLLECTION, 10801 University Boulevard, Manassas, VA 20110-2209 (EFFECTIVE MARCH 23, 1998)

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicants' cooperation is requested in correcting any errors of which applicant may become aware.

3. Rejections

3.1. 35 USC, section 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

Claim 28 is rejected under 35 U.S.C. 101 because the disclosed invention is inoperative and therefore lacks utility. The claim is directed to a process for the production of vitamin B₁₂ (cobalamin), comprising culturing a host cells containing a polynucleotide that does no contain a gene allowing for cobalamin production, so called **cob gene**. Said host cell is able to produce vitamin B₁₂ efficiently only when the *cob* gene is operably linked to a sequence controlling its expression (page 10, line 15). "The heterologous or endogenous gene may be inserted between nucleotides 1 and 200 or between nucleotides 1500 to 3555 of SEQ ID NO: 1"(page 10, line 22).

Claim 29 is included in this rejection because being dependent on the rejected base claim does not correct its deficiencies.

3.2. 35 USC, section 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 28 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 28 is rejected because the phrase "hybridizing selectively" renders the claim indefinite. The examiner noticed that Applicants exemplify hybridization conditions on page 4, line 11 and page 7, line 8 of the application. However, conditions are merely exemplified and there is nothing to suggest that other hybridization conditions are not intended to be included. In the art what conditions are applied for hybridization varies widely depending on the experiment and experimenter making the determination. Therefore, it is unclear how homologous to a sequence encoding SEQ ID NO: 1 a sequence must be so as to selectively hybridize to SEQ ID NO: 1, i.e., the scope of the claim is indefinite. Specifying the hybridization conditions in the claims will ablate this rejection.

Claim 28 is also indefinite because the claim recites in part d) the term "substantially homologous" that renders the claim indefinite.

The term "substantially homologous" in claim 28 is a relative term. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, therefore it is unclear how homologous to a DNA encoding SEQ ID NO: 2 or 3 or a fragment of either, a sequence must be to be within the scope of the claim. Thus, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Identifying the homology percent required, would ablate this rejection.

Claim 29 is included in this rejection because being dependent on the rejected base claim does not correct its deficiencies.

3.3. 35 USC, section 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3.3.1. Biologic deposit requirement

Claim 28 part b) and c) and claim 29 are rejected under 35 U.S.C. § 112, first paragraph, because the specification is lacking the description of biologic deposit. The invention appears to employ a novel 3.6 kb plasmid of *Propionibacterium freudenreichii* CBS 101022 and CBS 101023. Since the plasmid of *Propionibacterium freudenreichii* CBS 101022 and CBS 101023 is essential to the claimed invention, it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The enablement requirement of 35 U.S.C. § 112 may be satisfied by deposit of *Propionibacterium freudenreichii* CBS 101022 and CBS 101023.

The examiner noticed that the deposit of *Propionibacterium freudenreichii* CBS 101022 and CBS 101023 was made under the terms of the Budapest Treaty (page 2, line 21), therefore an affidavit or declaration by the applicant, or a statement by an attorney of record over his/her signature and registration number, stating that the specific microorganism has been deposited under the Budapest Treaty and that the strain will be irrevocably and without restriction or condition released to the public upon the issuance of the patent, would satisfy the deposit requirement made herein.

3.3.2. *Lack of written description*

Claim 28 and 29 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 28 is directed to a process for production of vitamin B₁₂ (cobalamin), comprising culturing a host cell containing a polynucleotide a sequence capable of hybridizing selectively to

- (a) SEQ ID NO: 1 or complement thereof;
- (b) a sequence from the 3.6. kb plasmid of *Propionibacterium freudenreichii* CBS 101022;
- (c) a sequence from the 3.6. kb plasmid of *Propionibacterium freudenreichii* CBS 101023; or
- (d) a sequence that encodes a polypeptide, which comprises a SEQ ID NO:2 or 3, an amino acid sequence substantially homologous thereto; or a fragment of either sequence.

The claim is directed to a genus of host cells containing said polynucleotide.

The specification however teaches only its representative species that is bacterium *E. coli* transformed with *Propionibacterium freudenreichii*/*E. coli* shuttle vector or bacterium *Propionibacterium freudenreichii* transformed with *Propionibacterium freudenreichii*/*E. coli* shuttle vector, or p545 plasmid or its 1.7 kb Fragment. The p545 plasmid or its 1.7 Kb fragment may be expressed only in

Propionibacterium genus.

Furthermore, the claim is silent as to the function of the genera of polynucleotide sequences listed under (a)–(d). The claimed genera encompass many sequences that are not useful in the claimed invention, because they do not possess the required functionality. The required functionality is to cause, when operatively linked, the expression of the gene necessary for synthesis of vitamin B₁₂.

Taking into account that the claim lacks the description of the host cell recited, as well as the description of the function of the nucleotide sequences comprised in said host, one skilled in the relevant art is not convinced the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 29 is included in this rejection because being dependent on the rejected base claim does not correct its deficiencies.

3.3.4. *Scope of enablement*

Even if one assumes the *cab* gene is contained in polynucleotide claimed in claim 28, the following rejection is proper.

Claim 28 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

- 1) transformants encompassing genus *Propionibacterium* and *E.coli*,
- 2) *Propionibacterium freudenreichii*/*E. coli* shuttle vector, and
- 3) p545 plasmid or its 1.7 kb fragment that may be replicated only in *Propionibacterium* genus,

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does not reasonably provide enablement for any host and any polynucleotide comprising a sequence capable of hybridizing selectively to

- (a) SEQ ID NO: 1 or complement thereof;
- (b) a sequence from the 3.6. kb plasmid of *Propionibacterium freudenreichii* CBS 101022;
- (c) a sequence from the 3.6. kb plasmid of *Propionibacterium freudenreichii* CBS 101023; or
- (d) a sequence that encodes a polypeptide, which comprises a SEQ ID NO: 2 or 3, an amino acid sequence substantially homologous thereto; or a fragment of either sequence.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The scope of the claim is not in accordance with the scope of enablement. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Otherwise, undue experimentation is necessary to make the claimed invention. Factors to be considered in determining whether undue experimentation is required, are summarized *In re Wands* [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the nature of the invention, (b) the breadth of the claim, (c) the state of the prior art, (d) the relative skill of those in the art, (e) the predictability of the art, (f) the presence or absence of working

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example, (g) the amount of direction or guidance presented, (h) the quantity of experimentation necessary.

The nature and breath of the claimed invention encompasses production of vitamin B₁₂ by culturing any host cell containing a polynucleotide comprising a sequence capable of hybridizing selectively to

- (a) SEQ ID NO: 1 or complement thereof;
- (b) a sequence from the 3.6. kb plasmid of *Propionibacterium freudenreichii* CBS 101022;
- (c) a sequence from the 3.6. kb plasmid of vitamin B₁₂ *Propionibacterium freudenreichii* CBS 101023; or
- (d) a sequence that encodes a polypeptide which comprises a SEQ ID NO:2 or 3, an amino acid sequence substantially homologous thereto; or a fragment of either sequence.

The specification provides an enablement (Example 5) how to produce vitamin B₁₂ by culturing *Propionibacterium freudenreichii* ATCC6207 transformed with the vector named pBRES36COB containing p545 plasmid sequence controlling replication, and the *cobA* (uroporphyrinogen III methyltransferase) gene from *Propionibacterium freudenreichii*. *E. coli* cells transformed with the pBRES36COB vector also produce vitamin B₁₂, however, the production is of no practical importance, because the frequency of *E. coli* transformation is very low. Thus, the scope of claim is limited to transformants of the genus *Propionibacterium*. The specification does not give examples or guidance how to transform other microbial, or mammalian, or plant cells

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with a vector based on p454 plasmid, so that these transformants produce vitamin B₁₂. Without further guidance as to the vector to be used for such transformation probability of success in making the claimed invention is very low.

Furthermore, the claim is directed to the extremely large and variable number of DNA sequences obtained from any natural or man-made source of DNA by hybridization to sequences a) - d). One skilled in the art knows that hybridization process selects a big number of DNA molecules comprising the ones not having the desired activity. The desired activity is to cause, after "operational linking", expression of the gene necessary for vitamin B₁₂ production. SEQ ID NO: 1 (plasmid p545) encompasses fragments that do not control its replication, and for that reason cannot be used for construction of expression vectors. Only the 1.7 kb fragment between Sall and AlwN1 restriction sites is important for replication.

In conclusion, without further guidance as to the particular fragment of SEQ ID NO: 1 to which a polynucleotide sequence should specifically hybridize, probability of success in making the claimed invention is very low. Thus, the experimentation left to those skilled in the art is improperly extensive and undue.

Claim 29 is rejected as depending on the base rejected claim, because it does not correct deficiencies of the claim from which it depends.

3.4. 35 USC section 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

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A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 29 is rejected under 35 U.S.C. 102(b) as being anticipated by the US Patent No. 5,545,538 (the patent) issued on August 13, 1996 to Ashai S. et al.

Claim 29 is directed to vitamin B₁₂ produced by a host transformed with a vector containing fragments of plasmid p545 of *Propionibacterium freudenreichii*, or sequences selectively hybridizing to sequences of said plasmid.

The patent discloses a method for production vitamin B₁₂ by cultivating a microorganism *Rhizobium cobalaminogenum*.

The products obtained by both methods are identical, unless Applicants proof the opposite.

4. Conclusion

No claim is in conditions for allowance, but claim 28 contains allowable subject matter. The following is examiner's reason for indicating allowable subject matter.

Applicants are first to disclose the p545 plasmid of *Propionibacterium freudenreichii*. The fragment of the plasmid responsible for its replication has been used for construction of a vector useful in efficient production of vitamin B₁₂ by fermentation of transformants of *Propionibacterium freudenreichii*.

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As allowable subject matter has been indicated, applicant's reply must either comply with all formal requirements or specifically traverse each requirement not complied with. See 37 CFR 1.111(b) and MPEP § 707.07(a).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (703) 305-7270. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m. If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (703) 308-3804. The fax phone number for this Group is (703) 305-3014. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.

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Patent Examiner



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